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WILL EXERCISE ADVICE BE SUFFICIENT FOR TREATMENT OF YOUNG ADULTS WITH PRE-HYPERTENSION AND HYPERTENSION? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Short Title: Exercise and Blood Pressure in Younger Adults

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ABSTRACT

Previous studies report benefits of exercise for blood pressure control in middle age and older adults, but longer-term effectiveness in younger adults is not well established. We performed a systematic review and meta-analysis of published randomized control trials with meta-regression of potential effect modifiers. An information specialist completed a comprehensive search of available data sources, including studies published up to June 2015. Authors applied strict inclusion and exclusion criteria to screen 9524 titles. Eligible studies recruited younger adults with a cardiovascular risk factor (with at least 25% of cohort aged 18 to 40 years); the intervention had a defined physical activity strategy and reported blood pressure as primary or secondary outcome. Meta-analysis included 14 studies randomizing 3614 participants, mean age 42.2+/-6.3 (sd) years. At 3 to 6 months, exercise was associated with a reduction in systolic blood pressure of –4.40 mmHg (95%CI, -5.78 to -3.01) and in diastolic blood pressure of -4.17 mmHg (95%CI, -5.42 to -2.93). Intervention effect was not significantly influenced by baseline blood pressure, body weight or subsequent weight loss. Observed intervention effect was lost after 12 months follow-up with no reported benefit over control, mean difference in systolic blood pressure -1.02 mmHg (95%CI, -2.34 to 0.29) and in diastolic blood pressure –0.91 mmHg (95%CI, -1.85 to 0.02). Current exercise guidance provided to reduce blood pressure in younger adults is unlikely to benefit long-term cardiovascular risk. There is need for continued research to improve age specific strategies and recommendations for hypertension prevention and management in young adults.

Key Words: Hypertension, High Blood Pressure, Exercise, Lifestyle, Meta-Analysis

INTRODUCTION

Population studies estimate 1 in 17 adults below the age of 40 years are hypertensive[1] with higher prevalence in those with diabetes, obesity, familial predisposition or prenatal and other early childhood factors.[2–7] Hypertension in early life significantly increases the risk of stroke and cardiovascular disease before the age of 50 years.[8–11] However, rates of diagnosis are consistently lower in younger adults and, even when identified, control is frequently sub-optimal.[5,12–14] This may relate to an acceptance of higher blood pressures due to a perceived lower 5 year cardiovascular risk, particularly for those in the pre-hypertensive range. This is despite epidemiological evidence of cumulative vascular protection and lower disease burden in later life following change in blood pressure and lifestyle during early adulthood.[9,15–17] Together these observations may explain why 1 in 5 strokes still occur in the under 55 year age group.[18]

To reduce burden of early stroke and cardiovascular disease, evidence based guidance is required to improve hypertension prevention and management for young adult populations. Exploring heterogeneity in response pattern to exercise and linking exercise response with hypertensive and cardiovascular phenotypes identifiable within younger subgroups may be of value in future studies and offer opportunity to deliver more personalised and targeted intervention strategies. Current guidelines recommend specialist review of young adults with elevated blood pressure since the risk of hypertension may be underestimated in the under 40 age group.[19] In the absence of significant end organ disease or secondary causes of elevated blood pressure, young adults under 40 years old are encouraged to implement lifestyle changes, in particular regular exercise, as the first line for hypertension management.[20,21] A limitation of this guidance is that it is based on data from physical activity trials in older populations with mean ages greater than 50 years.[22,23] There are a number of potential modifiers of intervention effect which are not consistent across age groups including baseline physical activity,[24] barriers to participation[25] and physiological training adaptations.[26] Therefore, we performed a new systematic review and meta-analysis to evaluate the quality of the evidence base and effectiveness of exercise intervention to reduce blood pressure in younger adult populations.

METHODS

Protocol registration: PROSPERO (www.crd.york.ac.uk/PROSPERO/) registration number CRD42014009604.

Search strategy and selection criteria

We completed a systematic review in accordance with established methods for Cochrane reviews of physical activity interventions (Supplement S1). We adhered to the Cochrane Handbook for Intervention Reviews and PRISMA statement (Supplement S2). An information specialist (NR) searched the following databases: Cochrane Central Register of Controlled Trials, MEDLINE & MEDLINE In Process, EMBASE, CINAHL, AMED, PsycINFO, SPORTdiscus, OpenGrey, Science Citation Index & Conference Proceedings Citation Index-Science, ACM Digital Library and IEEE Xplore Digital Library. Cochrane highly sensitive search was used to identify randomized controlled trials. No language or date restrictions were applied. Bibliographies of review articles and selected articles were examined for relevant trials. Literature searches completed up to June 2015. Full description of data sources and search summary available online (Supplement S1, Table S1).

Study selection and data extraction

We included studies with mean population age between 18 to 40 years old or within one standard deviation of this range to ensure at least 25% of the study population were younger than 40 years old. To be representative of young adults who may be provided advice to manage blood pressure, included studies were required to recruit participants with one or more cardiovascular risk factor, or family history of cardio-metabolic risk. Risk factors included hypertension or pre-hypertension (systolic blood pressure ≥ 120 mmHg and/or diastolic blood pressure ≥ 80 mmHg), overweight (mean body mass index(BMI) > 25 kg/m^2) but not severely obese (BMI ≥ 35 kg/m^2), diabetes, metabolic syndrome, dyslipidaemia, smoking and alcohol consumption. The defined BMI exclusion criteria were based on the understanding that severely obese populations have higher burden of comorbidities and potential functional barriers to exercise participation that makes them a unique target audience. Studies examined the effectiveness of interventions with defined exercise, physical activity or cardiovascular fitness components. The comparator was a control group exposed to placebo, no and/or minimal intervention. Blood pressure was reported as a primary or secondary outcome after a minimum follow-up of 3 months. Studies were required to have over 80% complete follow-up data analysing the results by intention-to-treat or, if not applying intention to treat, ensuring less than 20% study attrition. Additional details on inclusion criteria provided in online supplement (Supplement S1).

Titles and abstracts were screened independently by paired authors (WW, HR, AL, PK). Two authors (WW, HR) independently reviewed full text articles and extracted data. Study inclusion was agreed by consensus in discussion with other authors (CF, PL). Missing or ambiguous data was clarified with the corresponding author. We assessed risk of bias for studies that met inclusion criteria for meta-analysis using the Cochrane Risk of Bias Tool which was expanded to include risk areas specific for physical activity and blood pressure interventions (Supplement S1). Quality of included studies were summarised using the GRADE approach.[27]

Statistical analysis

Studies were analysed using mean and standard deviation (SD) of outcomes expressed in the original papers. Clinic blood pressures, measured at rest, were reported across all studies and used as the outcome measures. We expressed effect size using the mean difference between the post-intervention values of the randomized groups. If required we imputed standard deviations from standard errors and confidence intervals using methods described in the Cochrane handbook.[27] When studies investigated multiple interventions arms, intervention arms inclusive of exercise were included as individual intervention strata. Mean values were plotted with associated error bars using forest plots. Statistically significant results were identified as confidence intervals excluding a null effect and p value<0.05. Heterogeneity was assessed through examination of the forest plots and quantified using the I^2 statistic. I^2 statistics were graded according to Cochrane interpretation (>75% considerable/large heterogeneity). Reporting bias was assessed by plotting a funnel plot of intervention effect on blood pressure (Supplement S1).

We completed meta-analysis according to Cochrane methods,[27] using RevMan version 5.2 statistical software.[28] A random-effects model was the default to incorporate heterogeneity between studies, the inverse variance method was used to calculate the overall effect and standard error.[29]

Planned subgroup analysis of included studies was completed according to the following co-variants: 1) Baseline blood pressure, 2) Baseline weight 3) Delivery method, whether exercise was self-directed or supervised 4) Estimated contact time between participants and intervention, 5) Target intensity of exercise, 6) Change in weight following intervention (Supplement S1).

Meta-regression analysis was performed using the Wilson (2010) SPSS macro using IBM SPSS Statistics for Windows, Version 22.0.[30] Meta-regression was performed using a random effects model to examine whether study level covariates (potential effect modifiers) predict intervention effect on systolic and diastolic blood pressure between studies at 3 to 6 months follow-up. A priori the following factors where agreed for inclusion in the meta-regression model; 1) Mean arterial blood pressure (MAP) combining systolic and diastolic blood pressure, 2) Estimated contact time between participants and intervention 3) Target exercise intensity during intervention 4) Effect of intervention on weight loss calculated as the standard mean difference between intervention and control post intervention to allow comparison between studies reporting change in weight and body mass index (Supplement Figure S3a-b).

RESULTS

Results of Search

We screened 9524 titles and abstracts reviewing 786 full text articles (Figure 1). We identified 14 RCTs with 20 exercise intervention arms for inclusion, published between 1985 and 2015 (Table 1, Table S2). The RCTs randomized 3614 participants with a recognised cardiovascular risk factor, mean age 42.2 years (SD 6.3). Over 75% of participants were Caucasian and only 35% were female (Table 1). The studies recruited pre-hypertensive and stage 1 hypertensive participants. The majority of stage 1 hypertensives were not medicated at time of intervention, one study included participants that continued with antihypertensive prescription (n=15).

Excluded studies, with explanation of exclusion listed in online supplement (Table S3). The major reason for study exclusion was age of population outside inclusion criteria (n=323) (Figure 1). 158 of these studies reported blood pressure as a primary outcome, of these, 73 studies excluded participants below 35 years old. None of the excluded cardiovascular studies performed subgroup analysis separating intervention effects by age. Other common explanations for study exclusion included non-RCT design or lack of true exercise control arms (n=181), or study objectives focused on acute or short term exercise response, primarily in healthy participants (n=51).

Description of Included Studies

The majority of participants received a combined behavioural intervention with a defined physical activity strategy (Table S2). 18 intervention exercise arms targeted increase in moderate to vigorous physical activity, 12 intervention arms delivered structured, supervised aerobic exercise programmes in gym and group environments with intensity defined by baseline exercise testing. Seven trial intervention arms promoted self-directed increase in physical activity supported by regular group and individual counselling sessions. Behavioural counselling was delivered by multi-disciplinary professional groups. Contact time with the intervention in the first 3 months ranged from 5 to 48 hours, average 25 hours. The average in the first 3 months for studies reporting 3 to 6 month outcome was 30 hours (Table S2). The minimum follow-up for inclusion in the present systematic review was 3 months, 10 studies report 3 to 6 months follow-up data (15 intervention arms, n=2716). Five studies complete follow-up at three months and 6 studies report follow-up after 12 months (8 intervention arms, n=3023, Table S2).

Risk of Bias and Quality Assessment

The funnel plot of intervention effect on systolic blood pressure was symmetrical about the mean effect size line suggesting there was no particular study publication bias (Supplement Figure S1). Overall quality of the included RCTs using the GRADE approach suggests moderate quality data (Supplement Figure S2). In total, nine studies are downgraded secondary to study design and outcome reporting being unclear or at risk of bias with limited reporting of participant allocation methods and lack of clarification of blinding during outcome assessment. A significant limitation of the included studies was the lack of reference to published study protocols that adhere to the TIDieR template.[31] Only the Trials of Hypertension Prevention (TOHP) and ProActive UK studies consistently reference published study protocols (Supplement S3, Table S2).

Participant compliance with intervention and effect on cardiovascular fitness and weight

The majority of studies reported over 80% participant compliance with intervention at 3-6 months, recorded as attendance at supervised classes and group meetings, or achievement of behavioural targets such as self-reported minutes of activity. However, compliance with behavioural targets dropped to an estimated 40% beyond 12 months.

Eight intervention arms deliver exercise in combination with weight management, 4 of these interventions report a significant reduction in weight loss compared to control at 3-6 months (Supplement Figure S3a). Dietary assessment was undertaken using selfreport diaries over periods of 1 to 7 days. The majority of studies use diary cards as aids to behaviour change as opposed to assessing compliance, only three studies report the change in dietary intake. Mean cardiovascular fitness was reported from 14 intervention arms, the median increase was 12% improvement in peak exercise capacity (range 3% to 30%).

Intervention Effect on Blood Pressure

Forest plots for mean differences in systolic and diastolic blood pressure after 3-6 months of intervention are presented in Figure 2 (Supplement Figure S4a-b). Mean difference in systolic blood pressure was -4.40 mmHg (95%CI, -5.78, -3.01) and -4.17 mmHg (95%CI, -5.42, -2.93) for diastolic blood pressure when intervention was compared with control.

There are no significant differences between intervention and control group blood pressures when followed up at, or beyond, 12 months (Figure 2, Supplement S5a-b). Mean difference in systolic blood pressure -1.02 mmHg (95%CI, -2.34 to 0.29) and mean difference in diastolic blood pressure was –0.91 mmHg (95%CI, -1.85 to 0.02).

Subgroup Analysis

I^2 Statistic identified moderate to considerable heterogeneity across the studies (56% to 72%) at 3 to 6 month follow-up. Subgroup analysis did not provide a consistent explanation for heterogeneity between studies for both systolic and diastolic blood pressure. I^2 Statistic reduced to below 45% for systolic blood pressure when analysis was restricted to hypertensive groups, groups with baseline weight above 90kg and self-directed intervention. (Table 2).

Supervised aerobic exercise, higher exercise intensity and increased contact time with intervention were associated with larger reductions in systolic and diastolic blood pressures (Table 2). Reduction in diastolic blood pressure was significantly greater when comparing supervised (-5.43 mmHg [95%CI, -7.58, -3.28]) with self-directed exercise (-2.64 mmHg [95%CI, -3.20, -2.08]) and when intervention targeted higher intensity compared to moderate intensity. Blood pressure reductions appeared greater in association with over 4 kilogram weight loss, a weight loss threshold identified from previous systematic review.[32] However, observed differences did not reach significance (systolic BP -5.03 mmHg [95%CI, -6.89, -3.17] vs -2.61 mmHg [95%CI, -5.77, 0.55] and diastolic BP -4.77 mmHg, [95%CI, -6.54, -2.99] vs -2.95 mmHg [95%CI,-4.76, -1.13]). There were no significant differences in intervention effect when groups were separated as hypertensive or pre-hypertensive at baseline (Table 2).

Meta-regression

The a priori meta-regression model explained 50% of variance in intervention effect on systolic blood pressure. Increased intensity of exercise and hours of contact with the intervention were significantly associated with reduction in systolic blood pressure (Table 3). Baseline mean arterial blood pressure and standard mean difference in weight loss (Supplement Figure S3a) between exercise and control groups post intervention were not significant predictors of mean reduction in systolic blood pressure. The a priori model did not provide significant explanation for variance in diastolic blood pressure response.

DISCUSSION

This is the first systematic review to apply age criteria to evaluate the RCT evidence base to promote exercise to prevent and manage hypertension in younger adults. In the short-term (3 to 6 months), exercise and physical activity interventions are beneficial, with between 4 to 5 mmHg reductions in blood pressure. This is a larger effect than reported from a recent review reporting results from older adult groups and pre-hypertension groups.[22] This may be explained by selection criteria, we excluded normotensive cohorts with no cardiovascular risk factors. Alternatively, the result may suggest that younger adults may be more responsive to exercise as an intervention to lower blood pressure. There were also comparable benefits in blood pressure reduction for both prehypertension and hypertension groups which has not been observed previously in older adult groups.[22] Early adulthood may be an important life stage to target cardiovascular risk reduction. It is identified as a period where at risk groups present with hypertension.[7] In addition, adverse cardiovascular risk profiles in early adulthood are predictive of future morbidity.[17,33,34] Transition to early adulthood is identified as a period of decline in physical activity,[35] with low fitness in early adulthood predictive of cardio-metabolic dysfunction in middle age[36,37]. In contrast, maintained or increased cardiovascular fitness in younger adults can change cardiovascular risk trajectory[16,38]. However, a dominant finding is that we have not observed any sustained effects in blood pressure reduction from studies reporting outcomes after 12 months. This is the first review in the blood pressure literature to explore the sustained effects of exercise intervention and the first to exclude studies with less than 3 months follow-up, which may have previously contributed to overestimation of effect.[22,39] Our reported findings are similar to patterns observed in the general physical activity literature with a longitudinal decline in compliance with maintaining physical activity. The current evidence supports the need to build more detailed physical activity recommendations for hypertension management in younger adult populations.

Current guidelines recommend review of adults under 40 years of age with elevated blood pressure for exclusion of secondary causes of hypertension.[19] The age inclusion criteria for this review were defined to align with this practice. However, a major limitation is the paucity of studies recruiting younger adults. Hypertension in younger adults is complicated by high rates of under-diagnosis and, when identified, sub-optimal treatment.[5,12–14] These deficiencies may reflect broader misconception that younger age is sufficiently protective against cardiovascular risk.[5,12–14] This pattern is reflected in this review with an observed age bias for study recruitment in favour of older adults. The majority of excluded trials recruit cohorts over 50 years of age. In addition, over 46% of studies reporting blood pressure as a primary outcome excluded participants under 35 years of age.

Improved risk evaluation and interpretation of the benefits of blood pressure reduction may facilitate discussion on how to reform hypertension management for younger adults. An example is clinical interpretation of the reported 4 to 5 mmHg reduction in blood pressure, if this was sustained in a younger adult cohort with prehypertension, the estimated 5 year incidence of hypertension would reduce from 1 in 5 to 1 in 10.[40] This interpretation may be more beneficial than prediction of 10 year risk of cardiovascular events which is difficult in younger adults.[41,42] However, long-term benefits on cardiovascular endpoints can be estimated; a sustained 2 mmHg reduction in blood pressure could translate to 7% to 10% reduction in stroke and ischaemic cardiovascular event.[9] The major challenge is how to achieve sustained effect. In this review intervention effect dropped to 1 mmHg by 12 months with no significant difference compared to control.

To provide a platform to improve future intervention design we present an evaluation of study level characteristics that predict intervention effect at 3 to 6 months. With regards intervention strategy and delivery, both supervised and self-directed exercise achieve reduction in blood pressure, although effect was greater with supervised exercise. This may reflect a dose effect, supervised exercise was associated with increased exercise participation in the short-term. This group also achieved higher exercise intensity and increased cardiovascular fitness. However, higher volumes of planned contact time between participant and intervention, irrespective of intensity or self-directed exercise, was also associated with greater reduction in blood pressure at 3 to 6 months. Explanation for the subgroup analyses may relate to distinctions between physiological and behavioural influences of intervention. The exposure to higher exercise intensity may drive a mechanism for change in blood pressure distinct from low level activity. Self-directed and lower intensity exercise had relatively lower effects on diastolic blood pressure which is consistent with previous observations that blood pressure responses differ with intervention strategy.[22,23,32]

The finding that contact time, independent of intensity is associated with a positive influence on systolic blood pressure may support a beneficial effect of increased frequency of low to moderate activity. However, interpretation is limited without objective and repeated measures of physical activity behaviour which was not reported in studies with 3 to 6 month outcomes. Alternatively, planned contact, inclusive of telephone and remote contact may be a stimulus for sustained behaviour. Unfortunately, the pattern across studies is that as contact is withdrawn intervention effect declines. This is despite several studies implementing recommended behaviour strategies such as promotion of participant self-efficacy, activity planning, self-monitoring and participant feedback.[25,43] Participant motivation and self-efficacy are of particular relevance as, despite the low attrition rates, the included studies report decline in scheduled attendance and compliance with intervention targets from over

80% at 3 to 6 month to 40% at 18 months. There are currently no strategies that effectively address the challenge of promoting sustained long term physical activity behavioural change. A promising approach is personalised intervention supported by device assisted behavioural change and flexible communication strategies to better sustain effective intervention.[43] The use of wearable activity monitors and physical activity tracking applications on mobile device can provide objective measures of behaviour, facilitate self-monitoring and allow real-time feedback. However, the resource demands of maintaining high contact time and technology supported behaviour change may be a barrier to clinical translation. Economic evaluation of effective interventions with reference to delivery cost and process evaluation of strategies to sustain participant engagement, motivation and compliance may help to drive innovation and overcome these barriers.

Improvement in intervention design and delivery may also benefit from more transparency and disclosure of the specific methods and content of delivered communication strategies. There were often only brief summaries available, which described the professional team, if communication training was provided to the team, and broad categorical descriptors of intervention themes discussed with participants. In the current review, a number of studies focused communication strategies around weight loss, promoting exercise as a mechanism for weight loss. However, an interesting observation from the review which may help to guide the evolution of future studies is the patterns of intervention effect associated with weight loss. Previous review identified that weight loss greater than 4kg was required to achieve significant blood pressure reduction.[32] However, in our review, short term benefits of exercise on blood pressure were seen even in those who did not achieve this degree of weight loss. This observation is supported by weight loss not being a significant effect modifier in the regression model. The positive message is that in the short term, exercise is beneficial for blood pressure reduction independent of pre or post intervention weight. Distinguishing between the independent benefits of exercise and weight loss may facilitate effective communication and participant engagement strategies, especially when participants may be motivated by different health and well-being goals.

Limitations

Major limitations are the paucity of research studies recruiting younger adult or performing subgroup analysis defined by age. Included studies did not present results by age preventing analysis of effect in very early adulthood. Evaluation of the available literature base would be strengthened by meta-analysis of individual participant data but this was outside the scope of the review. The results would be strengthened by using ambulatory blood pressures, only three studies reported ambulatory blood pressures in addition to clinic blood pressures. Identification of effective intervention components is limited by several study level factors including; lack of objective measurement and tracking of physical activity behaviour, limited description of content and delivery of communication strategies and lack of disclosure of effectiveness of intermediate intervention process outputs such as strategies to maintain participant engagement and compliance. In the majority of studies there is also risk of bias in relation to participant allocation concealment and blinding of outcome assessors, with methods not discussed or unclear, which may risk overestimation of intervention effectiveness. However, overall the quality of included studies were moderate and funnel plots suggest no evidence of reporting bias, though caution in interpretation is required because of the small number of studies.

Perspectives

This review raises concern that current clinical practice to promote lifestyle and exercise intervention risks suboptimal management of young adult hypertension. Although it has been pragmatic to assume that exercise will improve blood pressure in young adults, the available evidence suggests current intervention strategies do not maintain long-term benefit. Discussion with young adult patient and public groups highlight that lifestyle interventions remains an attractive alternative to starting potential lifelong prescriptions for blood pressure. However, short-term reduction in blood pressure reported in this review involved multiple contacts over time and delivery of targeted exercise prescription. These strategies generally required supervised exercise interventions which are expensive and currently not widely supported.[44] A major challenge for the clinical research community is to design and evaluate interventions which target sustained increase in physical activity behaviour, accommodate potential for titration of exercise prescription and deliver improvement in the cost per quality adjusted life year. Translation of research findings into clinical practice may be improved by study design incorporating comparative adaptiveness evaluations and exploring interactive effects with prescription medication. Going forward there appears to be a need for strategic overhaul of the approaches implemented in the prevention and management of young adult blood pressure.

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Novelty and Significance

What is New?

An age defined review of randomized trials, with long term follow up, designed to assess effectiveness of exercise intervention for blood pressure reduction in younger adults.

What is Relevant?

Exercise intervention is beneficial for young adults in the short-term at 3-6 months but has no sustained effect at, or beyond, 12 months. Efficacy of intervention at 3 to 6 months was dependent on intensity of exercise and contact time with intervention teams.

Summary

Current recommendations for lifestyle and exercise interventions risk undertreating younger adults. There is need for review of practice and development of affordable interventions that deliver appropriate dose of exercise and sustained behaviour change.

Table 1. Baseline description of study populations participating in RCTs included in meta-analysis

Study	Mean Age (sd)	Age Range	Female (%)	Weight kg (sd)	BMI kg/m^2	Intervention Group BP mmHg		Control Group BP mmHg	
						Systolic	Diastolic	Systolic	Diastolic
Duncan 1985	30·4 (.)	21-37	0	86·4 (14)	.	146·3(5·9)	94·3(4)	145(5·5)	93·3(3·8)
Stamler 1989	37 (3·5)	30-44	13	84·3 (11)	.	122·2(6·7)	82·4(2·8)	122·9(7)	82·6(3)
Blumenthal 1991 Aerobic Exercise	45·2 (7·8)	29-59	38	82 (13)	27	141(9)	96(6)	142(12)	96(6)
Blumenthal 1991 Strength	45·2 (7·8)	29-59	42	81 (15)	27·2	143(10)	95(5)	142(12)	96(6)
Stevens 1993 TOPH Weight Loss & Exercise	42·8 (6·1)	30-54	32	89·7 (13)	29·5	124·3(8·4)	83·7(2·6)	124·6(8·1)	84(3)
Whelton 1997 TOHP Combined Lifestyle	43·6 (6·2)	30-54	31	93·6 (14·2)	.	127·4(6·5)	86(1·9)	127·3(6·4)	85·8(1·9)
Whelton 1997 TOHP Weight Loss and Exercise	43·4 (6·1)	30-54	37	93·4 (14·1)	.	127·6(6·1)	86(1·9)	127·3(6·4)	85·8(1·9)
Blumenthal 2000 Aerobic exercise	46·6 (8·8)	>29	54	95·4 (14·5)	32·8	138·1(15·4)	93·6(7·3)	143·8(6·9)	94·4(3·4)
Blumenthal 2000 Aerobic exercise and Weight	48·5 (8·9)	>29	62	93·3 (17·7)	32·1	142·7(10·4)	93·2(5·2)	143·8(6·9)	94·4(3·4)
Tsai 2002	41 (8·6)	20-60	45.2	.	23·6	134·3(12·2)	85·3(10·2)	137·6(7·9)	91·6(7·9)
Esposito 2003	34.6 (5)	20-46	100	94.5 (9.3)	34.8	124(8.5)	85(4.7)	123(7.9)	85(4.9)
Olson 2006	38 (6)	24-44	30	38 (6)	27.6	119(7.7)	67(7.7)	119(11.6)	68(11.6)
Kinmonth 2008 In Person	40.6 (6)	20-50	62	78.6 (15.6)	27.7	122.6(12.6)	77.9(9.0)	122.6(12.6)	78.2(9.0)
Kinmonth 2008 Telephone	40.6 (6)	20-50	62	79.9 (18)	27.8	124.2(13.0)	79.1(10.6)	122.6(12.6)	78.2(9.0)
Marquez-Celedonio 2009	43·2 (7·8)	30-55	.	78·1 (15)	31·2	133·0(4·4)	87·6(2·84)	132·7(4·2)	85·6(4·1)
Knoepfli-Lenzin 2010 Football	37 (4)	20-45	0	82·1 (8·7)	26	134(7·0)	87(4·0)	134(4·0)	86(3)
Knoepfli-Lenzin 2010 Running	36 (5)	20-45	0	87·3 (9·4)	26	136(9·0)	87(5·0)	134(4·0)	86(3)
Edwards 2011 Aerobic Exercise	45·9 (10·4)	25-65	50	.	30·1	140·6(9·8)	89·8(11·2)	137·6(11·5)	88·2(9·2)

Edwards 2011 Aerobic Exercise and Weight Loss	45·9 (10·4)	25-65	50	.	31·2	139·9(10·5)	85·1(10)	137·6(11·5)	88·2(9·2)
Krustrup 2012	46 (7.3)	31-54	0	97·8 (13·6)	30	151(10)	92(7)	153(8)	96(6)

Mean values presented with standard deviations (sd). Gender distribution presented as percentage of females included. BMI: Body Mass Index (kg/m^2). Missing or unreported values represented as (.).

Table 2. Subgroup analysis of effects of intervention on systolic and diastolic blood pressure according to study level characteristics.

Group	Intervention Arms	N	Systolic BP, mmHg	Diastolic BP, mmHg
Overall Intervention effect≤6months follow-up	15	2716	-4·40 (-5·78, -3·01) I^2=56%, Z=6·22 (p<0·00001)	-4·17 (-5·42, -2·93) I^2=72%, Z=6·57(p<0·00001)
Intervention effect ≥ 12months	8	3023	-1·02 (-2·34, 0·29) I^2=64%, Z=1·53 (p=0·13)	-0.91 (-1·85, 0·02) I^2=62%, Z=1.92 (p=0·06)
Baseline Weight <90kg	7	815	-3·0 (-6·04, 0·05) I^2=72%, Z=1·93 (p=0·05)	-3·88 (-6·13, -1·63) I^2=73%, Z=3·38 (p=0·0007)
≥90kg	5	1806	-4·23(-5·49, -2·98) I^2=32%, Z=6·6 (p<0·00001)	-3·69 (-5·09, -2·30) I^2=69%, Z=5·2 (p<0·0001)
Baseline Systolic BP<140 mmHg and Diastolic<90 mmHg	7	2370	-4·41 (-6·06, -2·77) I^2=69%, Z=5·25 (P<0·00001)	-3·87 (-5·33, -2·41) I^2=77%, Z=5·20 (P<0·00001)
Baseline Systolic BP≥140 mmHg and or Diastolic≥90 mmHg	8	346	-4·35 (-7·26, -1·44) I^2=42%, Z=2·93 (P=0·003)	-4·55 (-6·91, -2·19) I^2=62%, Z=3·78 (P=0·0002)
Aerobic Supervised Exercise (follow-up≤6months)	11	475	-5·40 (-8·08, -2·72) I^2=56%, Z=3·95 (p<0·0001)	-5·43 (-7·58, -3·28) I^2=67%, Z=4·95 (P<0·00001)
Self-directed physical activity (follow-up≤6months)	3	2199	-3·81 (-4·52, -3·09) I^2=0%, Z=10·39 (p<0·00001)	-2·64 (-3·20, -2·08) I^2=0%, Z=9·18 (p<0·00001)
Weight Loss>4kg	6	1586	-5·03 (-6·89, -3·17) I^2=65%, Z=5·31 (p<0·00001)	-4·77 (-6·54, -2·99) I^2=79%, Z=5·27 (p<0·00001)
Weight Loss≤4kg	6	1236	-2·61 (-5·77, 0·55) I^2=61%, Z=2·07 (p=0·11)	-2·95 (-4·76, -1·13) I^2=53%, Z=3·18 (p=0·001)
Moderate exercise intensity (≤ 60%)	5	2265	-3.40 (-4.59, -2.21) I^2=50%, Z=5.60 (P<0.0001)	-2.58 (-3.13, -2.03) I^2=0%, Z=9.14 (P<0.00001)
Moderate to Vigorous intensity (>60%)	10	451	-6.19 (-8.64, -3.73) I^2=43%, Z=4.93 (P<0.0001)	-5.92 (-8.09, -3.76) I^2=64%,Z=5.36 (P<0.00001)
Contact time less than 60 hours	9	806	-2.83 (-5.33, -0.34) I^2=46%, Z=2.23 (P=0.03)	-3.91 (-6.33, -1.49) I^2=67%, Z=3.16 (P=0.002)
Contact time 60 hours or more	6	1910	-5.61 (-7.55, -3.67) I^2=69%, Z=5.68 (P<0.00001)	-4.57 (-6.22, -2.92) I^2=80%, Z=5.42 (P<0.00001)

Results at 3 to 6 month follow-up used unless otherwise stated. Mean differences are pooled estimates from meta-analysis with 95% CIs. I^2 values reported as measure of heterogeneity. Z scores with associated p values reported as test for overall effect.

Table 3. Meta-regression model comparing effect of study level covariates on post intervention systolic (1) and diastolic (2) blood pressure (mmHg) compared with control.

	Model 1. Systolic Blood Pressure			**Model 2. Diastolic Blood Pressure**		
Variable	**$\beta_1 \pm$ SE**	**CI (95%)**	***Z(p)***	**$\beta_1 \pm$ SE**	**CI (95%)**	***Z(p)***
MABP (mmHg)	0.3161 ± 0.1625	-0.0230, 0.6346	1.95 (0.052)	-0.0255 ± 0.1966	-0.4108, 0.3599	-0.13 (0.897)
Hours of Contact	-0.0718 ± 0.0336	-0.1376, -0.0060	-2.14 (0.032)	0.0192 ± 0.0404	-0.0601, 0.0985	0.47 (0.635)
Exercise Intensity	-0.1458 ± 0.0601	-0.2636, -0.0281	-2.43 (0.015)	-0.1275 ± 0.0724	-0.2695, 0.0144	-1.76 (0.078)
Weight Loss	-0.9610 ± 1.6473	-4.1897, 2.2677	-0.58 (0.560)	2.1510 ± 1.9962	-1.7615, 6.0635	1.08 (0.281)

Model statistics for systolic blood pressure $R^2 = 0.50$, Q =16.4, df 4.0, p=0.0025.

Model statistics for diastolic blood pressure $R^2 = 0.23$ Q =4.95, df 4.0, p=0.293.

Notes: MABP Mean Arterial Blood Pressure at baseline (mmHg); $\beta_1 \pm$ Standard Error;

CI (95%), 95% confidence intervals; *Z(p)*, *z*-score and alpha value.

Figure Legends

Figure 1. PRISMA flow diagram describing the screening and selection of studies for inclusion in meta-analysis.

Figure 2. Forest plot demonstrating mean difference in systolic and diastolic blood pressure (mmHg) after 3 to 6 months (A & B) and at, or beyond 12 months (C & D) follow-up. Included studies are all randomized control trial design delivering exercise and physical activity lifestyle intervention. Results for individual exercise intervention arms reported when available. Squares represent mean difference between intervention and control post intervention with 95% CIs, size of the square proportional to the weight of the study; pooled estimates from meta-analysis are depicted as solid black diamonds.